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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,333	05/24/2005	Edith Dellacherie	122536	8802

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EXAMINER	
PALENIK, JEFFREY T	
ART UNIT	PAPER NUMBER
1615	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,333	DELLACHERIE ET AL.	
	Examiner	Art Unit	
	Jeffrey T. Palenik	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24 and 28-31* is/are pending in the application.

4a) Of the above claim(s) *8,19 and 21-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-18,20 and 28-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendments and remarks filed 13 December 2008 are acknowledged and entered on the record. The Examiner acknowledges the following:

No claims have been cancelled.

Claims 28-31 have been added. Support for the claims is found in Applicant's originally submitted claims 9, 3, 4 and 17, respectively.

Claims 1-7, 9-18 and 20 have been amended. Claim 1, in particular, has been amended to include the limitation "wherein the hydrophobic groups are anchored in the polymeric core of the particle". The amendment is supported by Applicants' disclosure. However, the newly amended limitation is considered by the Examiner to be a property which results from coating the biodegradable polymer core with a hyaluronan-based coating and until some material difference in the properties of the composition are demonstrated, said limitation is considered by the Examiner to be directed toward the instantly claimed composition.

The amendments to claims 3, 4, 9 and 17 are supported and are discussed below.

The remaining amendments made to claims 2, 5, 6-8, 10-16, 18 and 20 were editorial in nature and added no new matter.

REQUEST FOR REJOINDER

Applicants' request for rejoinder for non-elected claims 8, 19 and 21-24 based on the allowability of the previously elected product claims has been fully considered, but is not persuasive. Since the presently elected claims are not considered to be in condition for allowance, it follows that the non-elected claims remain presently withdrawn from consideration.

Thus, claims 1-7, 9-18, 20 and 28-31 now represent all claims currently under consideration.

INFORMATION DISCLOSURE STATEMENT

No new Information Disclosure Statements (IDS) have been submitted for consideration.

WITHDRAWN OBJECTIONS/REJECTIONS

Objection to the Claims

Applicants' amendment to claim 9, narrowing the scope of the biodegradable polymer to synthetic, has been considered fully and is persuasive. Thus, said objection has been **withdrawn**.

Rejection under 35 USC 112

Applicants' amendments to claims 1, 3-5, 12, 15 and 17, render moot their rejections, under 35 USC 112, second paragraph.

Claim 1 has been amended, in addition to the aforementioned, to remove the phrases "is based on", "at least partially" and "the carboxylic".

Claim 3 has been amended to remove the phrase "which may be".

Claim 4 has been amended to remove the phrase "in particular".

The dependency of claim 5 has been changed from claim 1 to claim 4, thereby amending around the lack of antecedent basis rejection.

Claim 12 has been amended to clearly convey that the particle further comprises an active substance which is contained within the core.

Claim 15 has been amended to remove the phrase "product type".

Claim 17 has been amended to remove the more narrowly recited particle size range.

Thus, said rejections have been **withdrawn**.

MAINTAINED REJECTIONS

The following rejection is maintained from the previous Office Correspondence dated 14 August 2008 since the art which was previously cited continues to read on the rejected claims.

CLAIM REJECTIONS - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-7, 9-18 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ottoboni et al. (WO 98/48783) in view of Dellacherie et al. (FR 2794763; machine translation) and Illum (USPN 4,904,479).

The instant claims are drawn to a micro- or nanoparticle wherein the core of the particle is comprised of at least one biodegradable organosoluble polymer and has an amount of at least one amphiphilic hyaluronan derivative on its surface (claims 1-7, 9, 18 and 20). Claims 2 and 20 each recite limitations which are directed to product-by-process limitations, which per MPEP §2113, hold no patentable weight. Claims 3-7 recite limitations to the hydrophobic group(s) attached to the hyaluronan derivative of claim 1, further limiting the composition in terms of number of carbon atoms, type of chain and degree of esterification. Claims 10 and 11 each further limit the biodegradable organosoluble polymer component. The particle composition is recited as further encapsulating an active agent (claims 12-14). Claim 15 further limits the biological active substance to one which has been synthetically derived. The Examiner interprets the limitation "synthetic active substance" as broad and reasonably comprising a compound which has been "produced artificially" (see *Merriam-Webster Online Dictionary*). Claim 16 recites that the composition comprises up to 95% of an active substance and claim 17 further limits the size of the particle.

Ottoboni et al. teach a microparticle composition containing solid-core, microparticles having diameters within the range of about 1-10 microns (1,000-10,000 nm), an outer layer of a biologically compatible material and an inner layer comprising a biodegradable polymer (claims 1 and 4). The biological compatible coating (e.g. outer layer) is taught as being a biopolymer protein which may comprise materials such as glycosaminoglycan (claims 33, 34 and 36).

Ottoboni further defines glycosaminoglycans as including hyaluronic acid and chondroitin sulfate (pg. 5, lines 18-19). Claims 38-41 teach the biodegradable polymer as comprising synthetic polymers of polycaprolactone, polylactide, polyglycolide, or copolymers of caprolactone, lactic or glycolic acids. Claim 9 teaches the microparticles as containing a drug, which is interpreted by the Examiner to inherently teach that the particles comprise an amount of drug greater than 0% and less than 100% by weight of the composition.

Ottoboni does not teach the instantly claimed hydrophobic modifications made to the glycosaminoglycan proteins of the outer layer of the particles. Despite teaching the inclusion of a drug within the coated microparticle composition, no specific type or category of drug is expressly taught. Similarly, there is no express teaching of an upper limit of active substance of 95% by weight of the composition.

Dellacherie et al. teach a composition containing a modified hyaluronan which consists mainly of hyaluronic acid (HA) in which a proportion of not more than 50% of carboxylic acid groups are modified with aliphatic esters side-chains, each of which include at least 10 carbon atoms (claim 1). It is taught that derivatives of the invention have a rate of esterification which is usually at least 1%, and more specifically taught that modified hyaluronans may be obtained where the rate of esterification is approximately 4% for an 18-carbon alkyl chain (pg. 2, lines 7-8 and 19-21). The invention is further directed to the above compositions wherein the aliphatic branches range in length from 10-22 carbon atoms (pg. 4, line 29 to pg. 5, line 3). The composition is taught as containing living cells and/or growth factors (claim 8). Other active hydrophobic agents such as steroid hormones, antibiotics, and anesthetics, are also taught as

being incorporated (e.g. encapsulated) into the microsphere compositions (pg. 8, line 22 to pg. 9, line 18). Claims 9 and 10 teach that the esterified carboxylic groups is high enough to prevent dissolution of the composition in an aqueous salt solution, yet low enough to such that the modified hyaluronan swells in water like a hydrogel. Claim 11 further limits the composition of claims 9 and/or 10 such that the composition may take more specific forms such as microparticles or nanoparticles. The microsphere and nanosphere particles are further taught as not exceeding an average diameter of especially 500 microns (pg. 7, lines 26-30).

Dellacherie does not expressly teach the particle composition as being comprised of the biodegradable organosoluble polymers as instantly claimed. There is also no express teaching of an upper limit of active substance of 95% by weight of the composition.

Illum teaches microparticles based on at least one biodegradable organosoluble polymer (e.g. polystyrene) further characterized that said particles are surface-coated with at least one material hyaluronic acid and polymers that are esterified to produce suitable hydrophobic domains (col. 10, lines 34-41). The hydrophobic domains which may be attached are taught as including hydrophobic moieties such as esterified maleic acid groups (col. 2, lines 31-34). Claims 1 and 5 teach the microparticles as containing a drug, which is interpreted by the Examiner again, to inherently teach that the particles comprise an amount of drug greater than 0% and less than 100% by weight of the composition. Drugs taught as being administered from the microparticles include macrophage activating agents, anti-leukemia agents and immunosuppressants (col. 10, lines 10-22). Microparticle diameters are taught as being 60 nm (Example 3).

Illum does not expressly teach that the hydrophobic groups are specifically attached to the hyaluronan and thus the does not teach sizes of the alkyl chains attached or the degree to which esterification occurs. Hyaluronic acid is taught, however, not as an encapsulated active substance. Similarly, chondroitin sulfate and glucosamine are also not taught.

In view of the combined teachings of the prior art, one of ordinary skill in the pharmaceutical or biomedical art, at the time of the invention, would have been motivated to combine an outer coating comprising hydrophobically-modified (e.g. esterified) domains and hyaluronic acid as taught by Illum, and an esterified, hydrophobically-modified amphiphilic hyaluronan derivative as taught by Dellacherie et al. with a particle composition whose core is comprised of a biodegradable, organosoluble material and an active agent as taught by Ottoboni et al. Such would have been obvious in the absence of evidence to the contrary since it is further taught that the hyaluronic acid (e.g. glycosaminoglycan) outer layer surface of the microparticle composition, which is practiced by both Illum (col. 2, lines 31-34 and col. 10, lines 34-41) and Ottoboni et al. (pg. 5, lines 13-14 and pg. 9, lines 9-18), is capable of being chemically modified to adjust the hydrophilicity of the particle such that it could accommodate exposure to different environments such as blood (pg. 5, lines 13-14 and pg. 9, lines 9-18). Additionally, Dellacherie et al. and Illum teach that both hydrophilic and hydrophobic active substances, which may be incorporated into the microsphere composition thereby indicating that alterations to the degree of esterification to the hyaluronan component of the practiced invention will similarly impact the degree of hydrophilicity.

A person of ordinary skill in the art would have a reasonable expectation of success in

modifying a hyaluronan-based, glycosaminoglycan-coated microparticle composition of Ottoboni using the alkyl chain esterification taught by Dellacherie et al. since the combined teachings disclose the instantly claimed coated pharmaceutical particles.

None of the references expressly teach the upper limit of active substance of 95% by weight of the composition, as claimed by Applicants. Since the values and formats of each parameter with respect to the claimed composition are adjustable, it follows that each is a result-effective parameter that a person having ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. However, the claims (i.e. claims 1 and 5 of Illum, claim 9 of Ottoboni et al. and claim 8 of Dellacherie et al.) teach the presence of an active substance encapsulated within their respective compounds, thereby inherently teaching that more than 0% of the composition is dedicated to a contained non-specific, active substance. Thus, it would have been customary for an artisan of ordinary skill, to adjust the amount and type of active agent present in the composition, particularly in view of the varying degrees of coating hydrophilicity as practiced by Dellacherie et al. and Illum, in order to achieve the desired medicated composition. Thus, absent some demonstration of unexpected results from the claimed parameters, optimization of any of these parameters would have been obvious at the time of Applicants' invention.

RESPONSE TO ARGUMENTS

Applicants' arguments with regard to the rejection of claims 1-7, 9-18 and 20 under 35 USC 103(a) as being unpatentable over the combined teachings of Ottoboni et al., Dellacherie et al. and Illum et al. have been fully considered but they are not persuasive.

Applicants argue with respect to the instantly amended claim 1, that the applied references teach that there is a need to strengthen the intramolecular network of the material molecules to secure the coating to the particle surface.

In response, the Examiner respectfully submits that the scope of Applicants' amended claim 1 does not exclude the presence of other molecules within the hyaluronan-based coating composition. Ottoboni, as discussed above, teaches a microparticle, whose inner biodegradable polymer layer, is coated by an outer layer of a biocompatible material which comprises a proteinaceous material such as a glycosaminoglycan (e.g. hyaluronic acid). It is further suggested that said outer coating may be modified so as to be amphiphilic in nature, since it is expressly taught that the outer coating may also comprise a cross-linked amphiphilic biopolymer. As such, the teachings provided by the combined references, most prominently by claims 1, 6 and 34 of Ottoboni, are considered by the Examiner as continuing to read on the instant claim 1.

Regarding the subject matter of new claims 28 and 31, the Examiner points to the discussion of Ottoboni, which not only expressly teaches the instantly claimed particle size (claim 1), but the instantly claimed natural organosoluble biodegradable polymer (e.g. polylactide, polyglycolide, polycaprolactone and copolymers) as well (claims 38-41). Regarding the subject matter recited within the limitations of new claims 29 and 30, which state properties of the hyaluronan-based coating composition; until some material difference(s) in the properties

of the composition are demonstrated, said limitation is considered by the Examiner to be directed toward the hyaluronan-based coating, which is instantly claimed.

For these reasons, Applicants' arguments are found unpersuasive. The above rejection is hereby **maintained** as well as extended to new claims 28-31, since the subject matter recited therein is expressly taught by the combined references.

All claims under consideration remain rejected; no claims are allowed.

CONCLUSION

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

CORRESPONDENCE

Any inquiry concerning this communication or earlier communications from the

examiner should be directed to Jeffrey T. Palenik whose telephone number is (571) 270-1966. The examiner can normally be reached on 7:30 am - 5:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey T. Palenik/
Examiner, Art Unit 1615

/MP WOODWARD/
Supervisory Patent Examiner, Art Unit 1615